

Treating Chronic Pain in Gulf War Illness

Study Protocol and Statistical Analysis Plan

NCT #: 02378025

March 17, 2015

Attachment 3: Technical Abstract

Background: Many military personnel who participated in the Gulf War in 1990-1991 reported negative health consequences subsequent to their deployment. The most prevalent of these health consequences involves a triad of symptoms that include fatigue, pain and cognitive disturbances commonly referred to as "Gulf War Illness" (GWI). No clear, unifying patho-physiological disease process or effective treatments have yet been identified for GWI. Results from a diverse spectrum of research studies support the view that veterans with GWI are medically ill, but that the physiological abnormalities that contribute to their illness are not currently well understood nor sufficiently treated by conventional medicine. While the cause of GWI remains unknown, a potential link between GWI and autonomic nervous system (ANS) dysregulation has been suggested. Yoga has been suggested to exert its therapeutic effects through adjusting imbalances in the ANS. Yoga has been shown to be clinically effective in treating many of the physical symptoms typically found in GWI including chronic pain and fatigue. As chronic pain is perhaps the most prevalent and debilitating symptom of GWI we propose to target pain. Significantly for this application, no improvements in pain have yet been reported in any clinical trial involving GWI. Furthermore, no published studies have investigated yoga as an intervention in GWI.

Objectives: The primary objective is to investigate yoga for the treatment of chronic pain in veterans with GWI. A secondary objective is to provide veterans with skills in yoga breathing, postures, and meditation that can be used to promote health and well-being.

Hypothesis 1 (primary): a) The subjective experience of pain as measured by the Brief Pain Inventory-Short Form will be reduced at end of treatment in the group given a 10-week Yoga Treatment program compared to a Pain Support control group. b) This effect will be sustained across time and will be found at the end of the 24-week post treatment follow-up. **Hypothesis 2: (secondary).** Yoga will have beneficial effect on general wellbeing: Thus, compared to the control group, the Yoga Treatment Group will show benefits across a broad range of measures including quality of life, fatigue, and medication use. **Hypothesis 3: (exploratory).** Yoga treatment will lead to improved ANS function. Specifically, improvements in ANS function will be manifested by an increase in heart rate variability (HRV) that will be observed in patients from baseline to end of treatment compared to the control group. **Hypothesis 4: (exploratory):** Moderators of Response. Age, severity of symptoms at baseline, type of comorbidity (depression pain medication, fatigue, duration of illness, HRV, baseline estimate of likelihood of attending class), or any combinations of these may affect or "moderate" treatment response.

Specific Aims: **1.** To assess the efficacy of yoga in reducing chronic pain, and to determine if the health-related benefits of yoga persist after termination of the treatment program. **2.** To obtain symptom-based outcome measures for veterans with GWI, before and after randomization, to assess pain, fatigue, physical functional status and quality of life. **3.** To obtain measures of ANS function by monitoring HRV in order to assess its relationship to symptoms of GWI. **4.** To analyze the data to determine whether yoga treatment reduces symptoms of GWI including chronic pain, quality of life, fatigue, and medication use. Due to the variability of GWI, we will also perform statistical analyses to determine whether the treatment response is moderated by a range of baseline variables including mood, medication, fatigue, and duration of illness.

Study Design: The intervention to be tested is a 10-week Yoga Treatment program that has been specially designed for the treatment of chronic pain as experienced by veterans with GWI. One hundred (100) patients will be randomly assigned to one of two treatment groups: Yoga Treatment Group or a Pain Support control group. The control group has been carefully designed to control for many features of a yoga intervention. Patients in both groups will attend weekly classes for 10 weeks, followed by 6-month follow up testing. Monitoring will include periodic measures of pain, fatigue, quality of life, and ANS function.

Impact: Despite increasing demand from veterans for yoga and other forms of complementary and alternative treatments, the provision of yoga in veteran healthcare remains sparse. This is due in large part to a lack of randomized clinical trials capable of demonstrating the efficacy and safety of yoga for the treatment of conditions such as GWI. Such a demonstration would strengthen the case for offering yoga as a widely-available treatment for pain in GWI and would help promote yoga as part of integrative healthcare. This treatment trial is designed to begin to determine potential mechanisms of pain maintenance in GWI. If yoga leads to improvement in pain outcome, this would support performing a larger clinical trial of yoga for treating pain and other symptoms of GWI.

Attachment 4: Lay Abstract

Background: Many military personnel who participated in the Gulf War in 1990-1991 reported negative health consequences following deployment. The most common of these health concerns involves a triad of unexplained chronic symptoms (fatigue, pain and cognitive disturbances) commonly referred to as "Gulf War Illness" (GWI). No clear cause of GWI or effective treatments has yet been identified. Indeed, results from various research studies support the view that veterans with GWI are medically ill, but that the physical abnormalities that contribute to their illness are not currently well treated by medical practice. Yoga offers a potentially effective treatment for GWI and it has been shown in clinical trials to be effective in treating some of the most common symptoms of GWI including chronic pain, chronic fatigue, and negative mood. Yoga involves a combination of physical and mental exercises including controlled breathing techniques, postures, and meditation. One of the ways that yoga is suggested to exert its beneficial effects is by adjusting imbalances in the peripheral nervous system (the system that controls bodily functions including heart rate, digestion and respiration). A strong link between GWI and peripheral nervous system dysregulation has been shown. Interestingly some of the most common complaints of GWI are also symptoms typically associated with dysfunction of specific components of the peripheral nervous system such as dizziness, weakness, and digestive problems. However, there are no published studies that have looked at the beneficial effects of yoga in veterans with GWI. The **objective** of this proposal is to evaluate yoga as treatment for chronic pain in veterans with GWI. Chronic pain was chosen because it is one of the most common and debilitating symptoms of GWI and yoga was chosen since it has been found to be effective in treating chronic pain in other medical conditions. The yoga program has been specially designed by several members of the study team who are highly experienced in the rehabilitation of veterans using yoga. The yoga program includes a broad selection of techniques including breathing, postures, and meditation that have been selected due to their reported benefits in treating chronic pain and fatigue. **Design:** One hundred (100) patients with GWI will be recruited and assigned with equal probability to one of two treatment groups: Yoga Treatment Group or a Pain Support control group. Patients in the Yoga Treatment Group will attend once-weekly yoga classes for 10 weeks. Patients in the Pain Support group will attend once-weekly classes for 10-weeks in which they will learn mental and physical techniques to control their pain. This "active" control group is intended to control for some of the benefits that patients may gain from group membership. These benefits include the camaraderie of group membership as well as learning some techniques for pain management that would be learned from the group. Participants in both groups will be monitored closely using assessments of pain, fatigue, quality of life and nervous system function. At the end of the 10-week program, all participants will be tested every 2 months for a total of six months using the same assessments to gain an understanding of whether yoga has an enduring benefit. Results will be analyzed by comparing the yoga and control groups, with an emphasis on the effects of yoga on pain. **Application:** This research is relevant to all patients with GWI who have chronic pain. As pain is one of the most common symptoms of GWI occurring in approximately one third of all patients with GWI, the results could have a broad impact on this patient group. Ultimately, this research is designed to provide veterans with GWI with a comprehensive yoga program that is both safe and effective in treating their pain. Such programs are not usually available to veterans, largely due to the lack of evidence that yoga or other forms of complementary and alternative treatment are clinically effective. This pilot study aims to provide such evidence. If yoga is shown to be safe and effective for treating pain in GWI, the programs may be offered at venues such as the Veteran's Affairs Healthcare System which currently offers a limited number of such programs and which could promote yoga as part of an "integrative healthcare" approach. This is a new and growing approach to healthcare with a broader focus than conventional care. Due to the minimal resources needed to provide yoga programs it is likely that this approach could be rapidly adopted by healthcare providers who may be attracted by the relatively low cost of such a program which can be given in a class setting. Finally, this treatment trial has the potential to determine some of the mechanisms of pain in GWI, especially dysfunction in the peripheral nervous system. If yoga is associated with improvement in pain, this would support performing a larger clinical trial of yoga for treating pain and other symptoms of GWI.

Specific Aims and Hypotheses

Objectives

The objective of this study is to identify a yoga treatment protocol that will ease the burden of pain in veterans with GWI. A secondary objective is to provide veterans with skills in yoga breathing, postures, and meditation that can be used lifelong to promote their health and well-being.

Specific Aims

1. To assess the safety and feasibility of recruiting 100 veterans with Gulf War Illness (GWI) who have chronic pain to complete a study that involves randomization to a 10-week Yoga Treatment Group or a control Pain Support Group. We will assess the efficacy of yoga to bring about an improvement of pain that will be measured 9 times over the course of the study. The effects of yoga on pain will be determined using growth curve modeling across this extended time period.
2. To obtain symptom-based outcome measures for veterans with GWI, before and after randomization, to assess pain, fatigue, physical functional status and quality of life measures during treatment, at end of treatment and at 6-month follow-up.
3. To obtain measures of ANS function by monitoring HRV in order to assess its relationship to symptoms of GWI during treatment, at end of treatment, and at 6-month follow-up.
4. To analyze the data to determine whether yoga treatment reduces symptoms of GWI including chronic pain, quality of life, fatigue, and medication use. Due to the complexity and variability of GWI, we will also perform statistical analyses to determine whether the treatment response is moderated by a range of baseline variables including mood, medication, fatigue, or duration of illness.

Hypothesis 1 (primary). a) The subjective experience of pain as measured by the Brief Pain Inventory-Short Form will be reduced at end of treatment (EOT) in the group given a 10-week Yoga Treatment compared to the Pain Support Group. b) This effect will be sustained across time and will be found at the end of the 24-week post treatment follow-up.

Hypothesis 2 (secondary). Yoga will have beneficial effect on general wellbeing: Thus, compared to the control group, the Yoga Treatment Group will show benefits across a broad range of measures including quality of life, fatigue, and medication use.

Hypothesis 3 (exploratory). Yoga treatment will lead to improved ANS function. Specifically, an increase in HRV will be observed in patients in the Yoga Treatment Group from baseline to EOT compared to the control group.

Hypothesis 4 (exploratory). Moderators of Response; age, severity of symptoms at baseline, type of comorbidity (depression pain medication, fatigue, duration of illness, HRV, baseline estimate of likelihood of attending class, or any combinations of these) may affect or “moderate” treatment response.

Study Design

Our hypothesis will be tested in a three-year RCT of yoga for chronic pain among veterans identified with GWI following deployment during the first Gulf War. One hundred (100) participants will be recruited and evaluated on a wide variety of measures including neurological and functional parameters. All participants will meet study criteria for chronic pain and all will have at least two other symptoms from the fatigue and/or mood-cognition categories as outlined in the GWI case definitions by Fukuda et al. (1998). The primary dependent measure will be pain scores at the end of treatment (EOT), and secondary and exploratory analyses will be conducted on other indices.

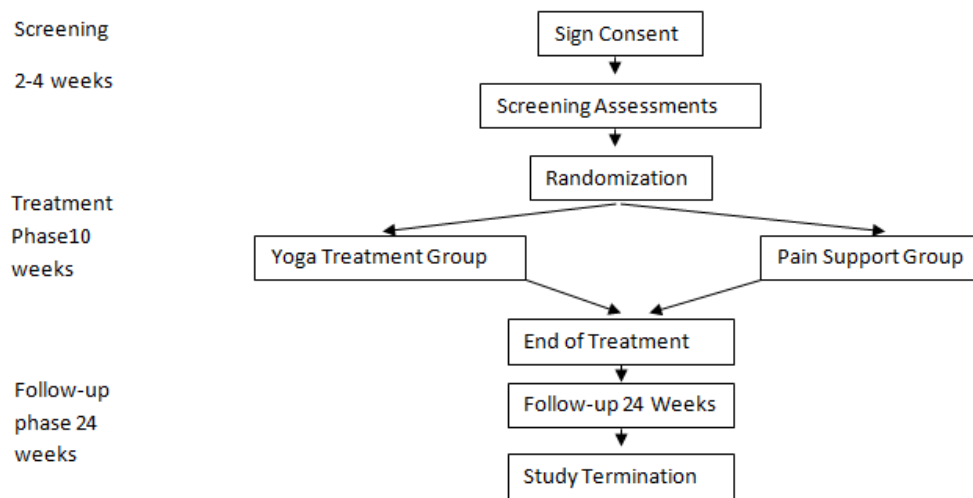


Figure 3: Overview of the experimental design and study procedures

Group Assignment and Randomization

Patients who sign the informed consent and meet the study eligibility criteria will be enrolled into the study and randomized into one of two treatment groups: the Yoga Treatment Group or the Pain Support Group. The primary and secondary hypotheses to be tested do not include interaction terms, so simple randomization will be used via a computer-generated table of random numbers to allocate the 100 patients to one of the two groups.

Case Definition of Gulf War Illness

The case definition for chronic multi-symptom illness as outlined in Fukuda et al., (1998) will be used to define GWI symptoms. According to this definition, a case is defined as having one or more chronic symptoms (present for ≥ 6 months) from at least two of the following categories: fatigue; mood and cognition (symptoms of feeling depressed, difficulty remembering or concentrating, feeling moody, feeling anxious, trouble finding words, or difficulty sleeping); and musculoskeletal (symptoms of joint pain, joint stiffness, or muscle pain). The symptom-category approach will be applied with the restriction that to be enrolled in the study, diagnosed patients will be required to have symptoms of chronic pain as outlined in the musculoskeletal category and at least two additional symptoms from the mood-cognition and/or fatigue categories.

Statistical Plan and Data Analysis

We will examine whether the Yoga Treatment Group will show more improvement, compared to the Pain Support Group in various outcome measures including pain, quality of life, and physical and mental health. The group comparison will be made in line with the principle of intention to treat. We will analyze the data using mixed effects (growth curve) modeling (Raudenbush & Bryk, 2002; Singer & Willett, 2003) fully utilizing outcome data repeatedly measured 9 times for participants completing assessments at all time points (baseline, 4 week, 10 week (EOT), and every 8 weeks during the 6 month follow-up assessments). For estimation of mixed effect models, maximum likelihood (ML) estimation will be used. For ML estimation of these models, the Mplus program version 6.11 or above will be used (Muthén & Muthén, 1998-2011). Data points that are missing due to subject attrition will be handled assuming that data are missing at random (MAR: Little and Rubin, (2002)) conditional on observed information, which is less restrictive than missing completely at random (MCAR: Little & Rubin, 2002) assumed in fixed effects analyses such as ANCOVA and regression analysis. In this procedure, all available cases including the ones with missing information will be included in the analyses. By including every subject who completed at least one assessment, we are not only more likely to conserve power, but also less likely to produce biased effect estimates. We expect about 30% attrition by EOT (10 week) and 45% by the 24 week follow-up (see Power Calculation below for justification of attrition rates). In mixed effects analyses, the change in the outcome will be modeled as the key dependent variable predicted by the treatment status and other relevant covariates. We will conduct the analysis with and without, conditional on relevant baseline covariates. The results

of these longitudinal analyses can be easily converted to group treatment effects at each assessment point to directly respond to our specific hypotheses. In particular, we are interested in the group difference at the end of treatment (10 week) and at the 24 week follow-up assessment.

The same analysis strategy focusing on mixed effects analysis will be employed for Hypotheses 1-3, where the focus is in examining group differences (i.e., treatment effect). In exploratory Hypothesis 4, we will examine whether baseline variables such as age or severity of symptoms will moderate treatment response. For this investigation, we will employ the MacArthur framework for moderator analysis. A moderator variable determines on whom or under what conditions the treatment (Yoga Treatment Group vs. control) affects the outcome differently. We will strictly follow the eligibility and analytical criteria for determining moderators described in Kraemer et al. (2008). All analyses will be conducted in the mixed effects modeling framework, where the McArthur framework will be embedded.

The reviewers suggest comparing the percent of participants that achieve a clinically significant reduction in pain (decrease of ≥ 1.75 points in the pain scale) across the two treatment groups using a chi-square test. This is an excellent suggestion and we will use this as a secondary outcome.

Inclusion/Exclusion Criteria

The inclusion/exclusion criteria are designed to identify patients with GWI who have chronic type pain as their defining feature and exhibit a full range of the manifestations of that condition. Furthermore, the study's sample is intended to be representative of the VA's pool of patients with GWI.

Identify inclusion criteria.

1. Born between 1936 and 1975 (ages 18 to 55 during Gulf War I).
2. Enlisted in armed forces between 1990-1991.
3. Patients must have symptoms suggestive of Gulf War Illness, including:
 - a. Chronic pain rated in the moderate to severe range on the SF-MPQ
 - b. At least 2 other symptoms in the mood-cognition and/or fatigue categories of GWI (as defined by the Fukuda et al. (1998) case definitions) manifested within the year after leaving the Gulf region.
4. If on a psychotropic medication regimen, that regimen will be stable for at least 4 weeks prior to entry to the study and patient will be willing to remain on a stable regimen during the 10 week acute treatment phase of the study.
5. Has an adequately stable condition and environment to enable attendance at scheduled clinic visits.
6. Able to read, verbalize understanding and voluntarily sign the Informed Consent Form prior to performance of any study-specific procedures or assessments.

Identify exclusion criteria.

1. Participation in another concurrent clinical trial.
2. Patients who are unable to visit the VA Palo Alto for study visits.
3. Patients who are unable to stand or walk.
4. Active current suicidal intent or plan. Patient at risk for suicide will be required to establish a written safety plan involving their primary psychiatrist and the treatment team before entering the clinical trial.

c. Informed Consent Process

The informed consent procedure will be conducted by the Study Coordinator at the VA Palo Alto. It is estimated it will last about 30 minutes but may take up to an hour if the potential participant has many questions. The office where consent will take place is located in the same building as the PI (Dr. Bayley), and other study team members (Dr. Ashford, Louise Mahoney) who will be available to answer any questions that the potential participant might have. First, the information contained in the written informed consent document will be explained verbally to prospective participants in language they can understand. Repetition will be used during the process if necessary. Special care will be taken to inform prospective participants that their participation is entirely voluntary and that they may withdraw at any time and for any reason without penalty or loss of currently existing benefits. Prospective participants will then be asked to carefully read the written informed consent form, and any questions will be answered. Next, the prospective participant will be asked to summarize the consent form with special focus on the discomforts, risks, and confidentiality sections. When prospective participants have demonstrated (by stating in their own words) that they understand the purposes, risks, and benefits of the study, they will be asked to initial each page and sign and date the last page. The Study Coordinator conducting the informed consent procedures will also sign and date the consent document, and the participant will be given a copy. The emphasis on the voluntary nature of participation is designed to minimize the possibility of coercion or undue influence to participate. If necessary, extra time will be given for potential participants to consider their involvement in the study.

d. Screening Procedures

To avoid unnecessary travel by veterans, a telephone pre-screening questionnaire will be given to those interested in participating in the study. The questionnaire will establish basic eligibility criteria (see Table 2 and “Telephone Pre-Screen Data Collection Form” in “Surveys.pdf”) (Note that such pre-screening questions can be given after obtaining verbal consent. Dr. Bayley (PI) was recruitment chair for a recent VA study using similar pre-screening procedures in which verbal consent was used). Veterans who pass the short phone screen will be scheduled for a full screening visit during which they will complete more extensive screening procedures listed in Table 2. The primary purpose of the screening is to establish eligibility for inclusion into the study and will be initiated after the patient signs the Informed Consent Form. Screening will normally be started on the same day as the consent visit. Depending on the participant’s availability, the screening phase will last up to four weeks to allow adequate time for all of the assessments to be completed, to assure the patient’s capacity and willingness to participate in the study and to ensure that all patients meet study criteria for chronic pain as well as two other associated symptoms of GWI identified in the inclusion criteria section for the study within seven days prior to randomization. Although screening data will not be used in the primary analysis, it will be retained to determine if participants who entered the study were comparable to those who were excluded.

Telephone pre-screen. To be given via telephone before the screening visit to establish eligibility related to several inclusion/exclusion criteria including age, military service, chronic pain, and presence of major neurological conditions.

Demographics Questionnaire. Self-report questionnaire to collect demographic, military and health characteristics.

SF-McGill Pain Questionnaire (SF-MPQ) (Melzack, 1987). A commonly used measure of clinical pain that is well-validated, reliable, and sensitive. It is a self-administered instrument containing 15 descriptors that yield scores of both sensory and affective components of pain. **Physical Exam.** This examination will be performed by the study Physician (Dr. Ashford) or an assistant and will include vital signs, height, weight, skin, ears (including gross hearing), eyes (including extra-ocular eye movements and retina), nasal passages, throat, neck, lungs, heart, abdomen, lymph nodes.

Clinical Questionnaire. This will ask about the presence, duration and intensity of 35 symptoms and is based on the clinical questionnaire used by Fukuda et al., 1998 which is the case study definition we have chosen.

Clinical Interview. This will be performed by the study Physician (Dr. Ashford) or an assistant and will review the answers to the clinical questionnaire. The interviewer will use these responses to decide whether the prospective participant meets the criteria for GWI as defined by Fukuda et al., (1998).

Evaluation	Eligibility Criteria
Telephone pre-screen	Served in first Gulf War and experiencing chronic pain
Demographics questionnaire	Born between 1936 and 1975 (ages 18 to 55 during Gulf War I)
SF-MPQ	Sensory and affective pain ratings in the moderate to severe range (2-3)

Physical Exam	Able to stand and walk without too much pain
Clinical Interview	Criteria for GWI as defined by Fukuda et al., (1998).
Clinical Questionnaire	GWI defined as having one or more chronic symptoms from at least 2 of 3 categories (fatigue, mood-cognition, and musculoskeletal)

Table 2. Screening evaluations used to establish eligibility criteria for study